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Fungal Burn Wound Infection

A 10-Year Experience

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• To evaluate our experience with fungal burn wound infection, we performed a 10-year review for comparison with our experience with bacterial burn wound infection. During the study period, a marked decline occurred in bacterial wound infection but not in fungal wound infection. Patients with either bacterial or fungal burn wound infection had massive injury, with burn size averaging greater than 50% of the total body surface area. Factors that appear to have markedly reduced bacterial burn wound infection, including patient isolation, topical chemotherapeutic agents, and burn wound excision, do not appear to have had a similar effect on fungal wound infection. The mechanism of spread and colonization of fungi, and the lack of effective topical chemotherapeutic antifungal agents, may explain in part our findings.

(Arch Surg. 1991;126:44-48)

The use of effective topical chemotherapeutic agents to reduce proliferation of microorganisms in the burn wound is one of several burn-specific treatments that have resulted in improved survival of burn patients during the past 50 years. The commonly used topical chemotherapeutic agents (mafenide acetate, silver nitrate, and silver sulfadiazine) have had a major influence in the reduced incidence of gram-negative burn wound infection, which, before the introduction of mafenide acetate in 1964, was the leading cause of death in burn patients treated at our institution.¹ In association with the use of effective topical chemotherapeutic agents, we have noted an increased incidence of "opportunistic" infections of the burn wound caused by yeasts and fungi.²

Serious fungal infections are rare in individuals with a normal immune system. They usually occur in patients who are immunosuppressed, either by a disease process or by a therapeutic intervention. Fungal infections are commonly reported in patients who have undergone transplantations

and in those with the acquired immunodeficiency syndrome, malignant neoplasms, and severe injuries as well as in critically ill patients who have received antibacterial antibiotic therapy.³ Burn injury also results in altered immune function, which is reflected in part by the development of anergy, tolerance to skin heterografts, and the decreased responsiveness of peripheral mononuclear cells to mitogenic stimuli.⁴ The magnitude of immunosuppression is related to the extent of burn injury. The alterations of immune function in the burn patient, along with the destruction of the skin barrier, appear to increase the susceptibility of the burn patient to fungal infections. A common site of fungal infection in the burn patient is the burn wound, and the most common fungal organisms that cause burn wound infection are those that belong to the classes Plectomycetes (*Aspergillus*), Blastomycetes (*Candida*), and Zygomycetes (*Mucor*, *Rhizopus*).⁵

We performed a 10-year review of our recent experience with fungal burn wound infection. During the same period, we noted a marked reduction in the incidence of bacterial burn wound infection. Herein, we describe the differences in management of bacterial and fungal wound infections and possible explanations for the differences in the incidence of bacterial and fungal burn wound infections during the study period.

PATIENTS, MATERIALS, AND METHODS

During a 10-year period (July 1979 to June 1989), 2114 patients with thermal injury were admitted to our burn center. The medical records and autopsy protocols of the patients were reviewed and form the basis of this study. Of the 2114 patients admitted, 209 (9.9%) developed histopathologically confirmed burn wound infection. Burn wound infection was defined as the histologic identification of microorganisms in viable tissue below or adjacent to the burn wound.⁶ With the patient under local anesthesia, biopsy specimens were obtained from areas of the burn wound suspected to be harboring infection (Table 1). The typical appearance of a wound harboring an invasive fungal infection is shown in Fig 1. The diagnosis of burn wound infection was confirmed by histopathologic (frozen-section or rapid permanent-section) examination of the biopsy specimen. A representative microscopic section that shows fungal burn wound invasion is shown in Fig 2.⁷ A portion of the biopsy specimen was also sent for culture. Representative samples of surgical and autopsy specimens of the burn wound were also submitted for permanent-section examination. The current scheme used to classify the depth of burn wound

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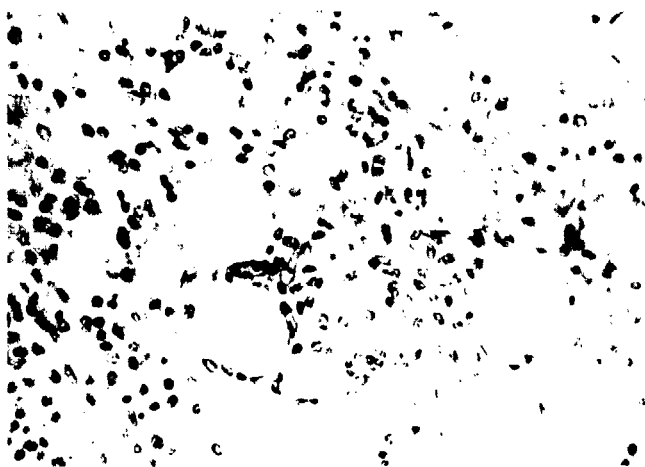
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Table 1.—Local Signs of Burn Wound Infection

Conversion of partial-thickness injury to full-thickness necrosis
 Focal or generalized brown, black, or violaceous discoloration of the burn wound
 Rapid separation of eschar layer
 Hemorrhagic discoloration of the subeschar tissue
 Green pigment in subcutaneous fat
 Red or black nodular lesions in unburned skin (ecthyma gangrenosum)
 Edema and/or red or black discoloration of unburned skin at the wound margin
 Centrifugal spread of subcutaneous edema with central wound necrosis



Fig 1.—Typical appearance of fungal burn wound infection. Note the discoloration of the wound.

Fig 2.—Fungal elements present in a biopsy specimen of the burn wound (stage 2b) (hematoxylin-eosin, $\times 300$).

colonization or infection is listed in Table 2.

Topical antimicrobial chemotherapy of the burn wound during the study period consisted of the alternating application of mafenide acetate in the morning and silver sulfadiazine in the evening. Prophylactic systemic administration of antibiotics was not used. Systemically administered antibiotics were used to treat infections diagnosed clinically or by blood culture. The type of antibiotic initially administered depended on the predominant organism encountered at our burn center at that time. Antibiotic therapy was subsequently guided by patient-specific culture, sensitivity reports, and the patient's response.

When gram-negative burn wound infection was diagnosed, mafenide acetate applied twice daily was used as the sole topical agent.

Table 2.—Classification of Microbial Status of Wounds

Stage 1: Wound colonization
 1a: Superficial colonization
 1b: Microorganisms in nonviable tissue
 1c: Microorganisms at the interface of viable tissue
 Stage 2: Invasive infection
 2a: Microinvasion of viable tissue
 2b: Deep or generalized invasion of viable tissue
 2c: Microvascular invasion

Therapy with systemically administered antibiotics, usually an aminoglycoside and a semisynthetic penicillin, was begun, and a semisynthetic penicillin (carbenicillin sodium) was injected twice daily into the subeschar tissue below the infected burn wound.⁸ If the infection was controlled by these measures and the patient's condition permitted, the involved area was surgically excised. Placement of autografts was usually delayed for several days following the burn wound excision, during which time the excised wound was covered with a biologic dressing.

Patients with invasive fungal infections were treated primarily by wide surgical excision of all of the infected tissue.⁹ Gentian violet,¹⁰ dilute 0.5% sodium hypochlorite (Dakin's solution), and 1% clotrimazole cream were used as antifungal topical chemotherapeutic agents in some patients. Systemic administration of amphotericin B was reserved for patients with clinically suspected or proved disseminated fungal infection or in those patients with microvascular (stage 2c) invasion, as identified on a histopathologic section of the burn wound.

RESULTS

Two hundred nine (9.9%) of the 2114 patients admitted during the 10-year study period developed burn wound infection based on histopathologic examination of the burn wound. Fungal burn wound infection occurred in 141 of these patients, and bacterial burn wound infection occurred in 68 patients. Patients with fungal burn wound infection had a mean age of 37 years and a mean burn size of 62.5% of the total body surface area (BSA); 47% of these patients had inhalation injury, and the mortality rate in this group was 74.5%. Patients with bacterial burn wound infection had a mean age of 32.6 years and a mean burn size of 54.4% of the total BSA; 51% of these patients had inhalation injury, and the mortality rate was 70.6%. The annual incidence of histopathologically documented bacterial and fungal burn wound infection is listed in Table 3. The annual incidence of fungal burn wound infection was relatively stable during the 10-year period, while there was a marked reduction in the incidence of bacterial burn wound infection beginning in 1983. Twenty-one of the patients with fungal burn wound infection died of disseminated fungal disease. The annual incidence of disseminated fungal disease is listed in Table 4.

The causative organism (species) for fungal burn wound infection could not be identified in every case due to the relatively low yield (approximately 30%) of recovery from tissue sample cultures.¹¹ In those cases in which a causative organism could be identified, either by culture results or by the characteristic morphologic appearance of the organism on microscopic examination, organisms found had the following frequencies: *Aspergillus* species and *Fusarium* species, 68%; *Candida* species, 18%; *Mucor* species and *Rhizopus* species, 9.1%; and *Microspora* species and *Alternaria* species, less than 5% each.

During the early part of the study period, three patients required amputation of an extremity to control the spread of fungal infection or to completely encompass all infected tissue, including one patient who required a hip disarticulation to control an invasive *Mucor* burn wound infection. During the last 30 months of the study, 24 patients were identified as having fungal burn wound infection. These patients were

Table 3.—Annual Incidence of Burn Wound Infection*

Year	No. of Admissions	Bacterial Burn Wound Infection	Fungal Burn Wound Infection
1979 (0.5 year)	140	9 (6.4)	7 (5)
1980	225	20 (8.9)	23 (10.2)
1981	229	12 (5.3)	6 (2.6)
1982	209	12 (5.7)	19 (9.1)
1983	188	3 (1.6)	15 (8)
1984	186	2 (1.1)	19 (10.2)
1985	197	2 (1)	10 (5.1)
1986	206	1 (0.5)	13 (6.3)
1987	221	3 (1.4)	11 (5)
1988	223	3 (1.3)	9 (4)
1989 (0.5 year)	90	1 (1.1)	9 (10)

*Values are number (percent of total admissions).

Table 4.—Annual Incidence of Disseminated Fungal Disease, 1979-1989

Year	No. of Cases
1979	1
1980	2
1981	1
1982	2
1983	2
1984	7
1985	1
1986	3
1987	1
1988	0
1989	1

treated with a consistent regimen of topical therapy (clotrimazole) and wound débridement. Disseminated fungal infection developed in only two of these patients, and none required an amputation to control the fungal infection.

In the 21 patients who died of disseminated fungal disease, the following visceral organs were involved: lungs (15 cases), heart (12 cases), kidneys (10 cases), brain (four cases), thyroid gland (one case), and liver (one case). Organisms caused disseminated fungal infection with the following frequencies: *Aspergillus* species, 71%; *Candida* species, 19%; and *Mucor* species, *Rhizopus* species, and *Fusarium* species combined, 10%. Six of the patients were noted to have fungal thrombophlebitis.

COMMENT

The patients who developed burn wound infection of either fungal or bacterial origin had massive injury, with an average burn size of 62.5% of the total BSA in the group with fungal infection and 54.4% of the total BSA in the group with bacterial infection. We also noted a high incidence of inhalation injury: 47% in the fungal infection group and 51% in the bacterial infection group. The severity of injury is reflected in the high mortality rate noted in each group: 74.5% in patients with fungal infection and 70.6% in patients with bacterial infection.

Burn wound infection was suspected when there was a characteristic change in the appearance of the burn (Table 1) or when blood cultures were positive for organisms that commonly cause burn wound infection. A rapid histologic technique was used to examine biopsy specimens of the burn

wound to confirm the diagnosis of burn wound infection. Cultures of the burn wound biopsy specimen were performed to assist in the identification of the causative organism but were not used to diagnose burn wound infection.

Burn wound infection, both fungal and bacterial, diagnosed by biopsy specimen and histopathologic examination, was treated with a combination of techniques that have been demonstrated to reduce mortality caused by both types of infection. For bacterial burn wound infection, this included systemically administered antibiotics, subeschar clysis of a semisynthetic penicillin, and the use of an absolute topical chemotherapeutic agent, mafenide acetate. Surgical excision of the involved tissue was performed if the patient's condition permitted. The excised wound was initially covered with a biologic dressing, and placement of autografts was delayed until there was no evidence of residual infection. This was done in an attempt to minimize loss of autograft due to proliferation of microorganisms in the wound bed. Control of the burn wound infection was documented by histopathologic examination of biopsy specimens obtained before surgery or of the tissue excised during surgical débridement of the wound.

Fungal wound infections were treated primarily by wide surgical excision of all infected tissue. Delays in the placement of autografts and use of biologic dressings were similar to that described for bacterial burn wound infection. Previous reports have described the frequent necessity to amputate to completely excise all the infected tissue to control aggressive fungal infections of the extremities.^{12,13} Early identification of fungal infection from biopsy specimens followed by appropriate surgical therapy has decreased the need for amputation to control progressive infection, as only three amputations were required during the study period.

During the study period, there was a marked decrease in bacterial burn wound infection but very little change in the incidence of fungal burn wound infection. The decrease in bacterial burn wound infection occurred in 1983. In 1982-1983, the protocol at our burn center was changed from an open-ward to an isolation (one bed per room) intensive care unit (ICU). During the opening of the new ICU, an admission and staffing plan was designed to prevent contact between patients admitted to the newly opened ICU and those who had been cared for on the open-ward ICU. The opening of the new facility was associated with the elimination of an endemic strain of *Pseudomonas* and an overall reduction in gram-negative infections.¹⁴ Improved isolation techniques, combined with effective topical chemotherapy and early excision and grafting of the burn wound, appear to have markedly decreased the incidence of bacterial burn wound infection in our unit.

The incidence of fungal burn wound infection, in contrast, remained remarkably stable during the same period. The true fungi are ubiquitous in the environment and can be cultured from heating and ventilation ducts, wound dressing supplies, laundry items, and plants and soil.¹⁵ *Candida* colonization of the burn wound appears to be primarily from endogenous sources.¹⁶ The spread of endemic strains of gram-negative bacteria occurs primarily via patient-to-patient contact or dissemination by the hospital staff. Fungi, yeast, and gram-positive bacteria appear to have an additional, airborne route of spread from the hospital environment. While the change to single-bed ICU rooms appears to have been effective in the cessation of mini-epidemics of gram-negative burn wound infection, it has not been as effective in decreasing the spread of fungi, yeast, and gram-positive organisms.

Despite the ubiquitous distribution of fungi in the hospital environment, serious fungal infections are quite unusual in the immunocompetent host.¹⁷ The massive burn injury of the

patients who developed fungal burn wound infection (62.5% of the total BSA) is associated with alterations in host defense mechanisms, including neutrophil function, lymphocyte subpopulation distribution, and immunoglobulin production.^{18,20} While none of the changes in immune function can be pinpointed as the cause of the increased susceptibility to infection that is observed in burn patients, it is probable that an association exists between these changes and the occurrence of fungal infections in the burn patient. At present, no technique reliably alters the immune system in the burn patient, other than the prevention of complications and the achievement of early wound closure. The use of systemically administered antibacterial antibiotics, which suppress normal flora and appear to increase the risk of fungal infections, should be reserved for documented infections and used only for the period necessary to control the infection.

Topical chemotherapy consisting of mafenide acetate, silver nitrate, or silver sulfadiazine is effective, in both experimental and clinical settings, in decreasing the proliferation of bacteria in the burn wound. No similar topical agent with proved effectiveness in experimental burn models is available to decrease the proliferation of yeast and fungi in the burn wound. Several topical antifungal chemotherapeutic agents may prove to be useful in burn patients. Clotrimazole, applied as a 1% cream, is an effective agent against *Candida* in patients without burns and is also useful in the treatment of dermal infections caused by dermatophytes²¹; it is not useful in the treatment of systemic fungal infections. Clotrimazole is poorly absorbed through normal skin, and its ability to penetrate the burn eschar is unknown. This agent was used to treat a number of the patients in this study, usually after a biopsy-proved diagnosis of fungal wound colonization (stage 1c) or fungal wound infection (stage 2) was made; it was not applied to the burn wound prophylactically. Nystatin is a polyene macrolide antibiotic similar to amphotericin B. It is available only for topical or oral use because of toxic effects associated with parenteral administration. It is effective against *Candida* species and most of the true fungi. In one study,²² nystatin (100 000 U/mL) mixed 1:1 with silver sulfadiazine was believed to effectively decrease the incidence of *Candida* burn wound infection and septicemia. In that study, the diagnosis of *Candida* burn wound infection was based in part on culture and not on histopathologic examination of the burn wound. Also, the criteria used to define sepsis were nonspecific and did not require positive blood cultures. Because of these factors, that study alone cannot be used to document the effectiveness of nystatin in the treatment of candidal burn wound infection. Moreover, the clinical effectiveness of nystatin against other fungi in burn patients remains unproved. The possibility that topical antifungal agents, such as nystatin, may interact with and alter or decrease the effectiveness of other topical agents when they are combined must be considered when such drug combinations are used.

Systemically administered amphotericin B should be used to treat patients who are suspected, on clinical grounds, to have disseminated fungal infection, who exhibit evidence of spread of fungal infection beyond the confines of the burn wound, or who have microvascular involvement detected on wound biopsy specimen (stage 2c). The use of amphotericin B may be associated with serious toxic effects, including fever, nephrotoxic effects, electrolyte disturbances, and hypotension.²³ Because of these toxic effects, amphotericin B should not be used to treat patients with localized fungal burn wound infection who do not exhibit evidence of either microvascular invasion or systemic disease. Prompt surgical débridement of the infected tissue should be performed in this setting. Several derivative forms of amphotericin B have been developed,

including liposomal amphotericin B and amphotericin B methyl ester.²⁴ These agents may be less toxic than the standard form of amphotericin and may also offer increased antifungal specificity. Promising results with these derivatives have been obtained in clinical trials.²⁵ Further evaluation will be necessary to enable widespread clinical use.

Other systemic antifungal agents include flucytosine, miconazole, ketoconazole, and fluconazole and are most often used in combination with amphotericin B in the treatment of systemic fungal infections caused by the Blastomycetes. Ketoconazole will penetrate the brain and cerebrospinal fluid and may be useful for fungal meningitis or a brain abscess.²⁶ Fluconazole has proved useful as single-agent therapy in the treatment of disseminated candidal and cryptococcal infections.²⁷ The effectiveness of these agents either alone or in combination with amphotericin B for disseminated fungal infection caused by the filamentous fungi remains unproved.

Our findings emphasize the need to perform histopathologic examination of the burn wound to diagnose the presence of burn wound infection. The yield of fungi from cultures of burn wounds is not high, even when fungi are visible on microscopic sections. Those organisms that are recovered by culture may take days or even weeks to grow, which severely limits the clinical utility of such a culture. Biopsy and frozen-section and rapid permanent-section analysis of the burn wound provide clinically relevant information on the microbial status of the wound and permit prompt institution of appropriate treatment.

Fungal burn wound infection, which currently occurs in approximately 7.5% of our admissions each year, is now the most common infectious complication involving the burn wound at our burn center. Factors that led to a decline in bacterial burn wound infection appear to have had little effect on the incidence of this complication. Early biopsy diagnosis of this complication, followed by the institution of appropriate therapy, primarily surgical débridement of the involved area, appear to have limited some of the adverse consequences of this complication, such as the need for amputation to control the infection and the development of disseminated fungal disease. This is documented by the low incidence of disseminated fungal infection and lack of need for amputation to control fungal infection during the final 30 months of the study period, during which a consistent treatment regimen was utilized. Fungal burn wound infection occurs most often in patients with extensive burn wound injury, who have a high mortality rate related to the extent of injury per se. The development and testing in experimental animal models of effective topical antifungal chemotherapeutic agents, followed by clinical trials of such agents, may enable the burn surgeon to identify means by which the proliferation of fungi in the burn wound can be controlled and the incidence of fungal burn wound infection reduced.

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Discussion

JOHN F. BURKE, MD, Boston, Mass: The Brooke experience is different from that usually reported in that the fungal infections reported in the literature are almost all *Candida* rather than other forms and were restricted to bloodstream infections with very few burn wound infections. Why does this difference exist? Were the people at Brook making the diagnosis more accurately or was there another reason? Because *Aspergillus* is a prominent player in the Brook report, one wonders about the air handling systems, as *Aspergillus* is a notorious creator of problems there.

DR AHRENHOLZ: Have the authors identified risk factors in the

development of fungal infection? What is the role of serial prospective wound biopsies?

DR LINEAWEAVER: What is your current topical therapy, and what concentration of Dakin's solution was used?

DR WALTER: There are three sources of fungi: leaky plumbing, rugs, and, the major one, air handling. The problems created by fiberglass in ducts and its interaction with high and low humidity are factors to be considered.

DR PECK: What fungal prophylaxis do you employ, and what topical anti-microbial treatment do you use?

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